Effects of Atorvastatin on Myocardial Ischemia-Reperfusion Injury and Ventricular Remodeling in Rats

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Abstract

Objective: To investigate the protective effects of atorvastatin on multiple organs and ventricular remodeling during myocardial ischemia-reperfusion in rats. Methods: 45 rats were randomly divided into 3 groups with 15 rats in each group, including atorvastatin group, ischemia reperfusion group and sham operation group. After completing the vegetation of myocardial ischemia-reperfusion injury model of rats, 8 rats were selected from atorvastatin group and ischemia-reperfusion group respectively, and were stained with Evans blue and TTS. Then, image analysis software was used to calculate the infarct area. The myocardial tissue of vegetation rats was homogenized, and MDA content was determined by TBA method. The contents of TNF-α and MPO were determined by ELISA. The hemodynamic indexes and key indexes of ventricular remodeling in the remaining rats were detected and analyzed 14 days after surgery. Results: Comparing the atorvastatin group with the reperfusion group, it was found that the myocardial infarction area in the atorvastatin group was smaller, and the myocardial infarction area without ischemia was larger, and the ratio of myocardial infarction area to the total ischemic area was significantly smaller than that in the reperfusion group (p<0.05). MDA, TNF-α and MPO were significantly increased in the ischemia-reperfusion group and atorvastatin group compared with the sham operation group, but the increase was less in the atorvastatin group. Compared with the ischemia reperfusion group, the hemodynamics and left ventricular function remodeling improved significantly (p<0.05). Conclusion: Atorvastatin can effectively reduce the infarct size after ischemia reperfusion palpitation, improve the hemodynamics and left ventricle, achieve multi-organ protection, conducive to ventricular remodeling, and can be used in clinical application.

Keywords

Atorvastatin, Rat, Myocardial ischemia, Reperfusion injury, Ventricular remodeling

1. Introduction

Statins, HMg-Co A reductase inhibitors, act specifically as rate-limiting enzymes in cholesterol synthesis, inhibit cholesterol synthesis, and enhance the activity of low-density fat egg white (LDL) receptors, thereby accelerating the clearance of LDL -- C in the serum. Studies have confirmed that statins have pleiotropic effects on cardiovascular protection, with many non-lipid-lowering effects, including improving vascular endothelial function, reducing
vascular inflammatory response, inhibiting smooth muscle proliferation and immune regulation [1]. Reperfusion therapy of ischemic myocardium is one of the main therapeutic methods for ischemic heart disease, and the associated ischemia-reperfusion injury becomes an important factor affecting the curative effect. Studies have shown that atorvastatin has protective effects on acute renal failure, renal tubule fibrosis and angiotensin ii-mediated renal injury. This study focused on the changes of central, liver and kidney function during myocardial ischemia-reperfusion in aged rats and the effects of statins on these changes.

2. Objects and methods

2.1 Research object

Forty-five rats were randomly divided into 3 groups with 15 rats in each group, including atorvastatin group, ischemia reperfusion group and sham operation group. The drug reagents used include atorvastatin, triphenyltetrazole chloride; Evans blue, formaldehyde solution. The experimental instrument used RM6240 multi-channel physiological signal acquisition system, animal ventilator DH-140B, Image Pro image analysis software, automatic biochemical detector, and prepared 1%TTC solution [2].

2.2 Methods

2.2.1 Group administration

The rats were fed in the experimental Animal Center of our hospital for 10 months to 20 months of age. After numbering and weighing, the rats were randomly divided into elderly control group, high-dose atorvastatin group and low-dose atorvastatin group, with 15 rats in each group. After atorvastatin was made into powder, normal saline was added to make suspension. The atorvastatin group was given 10 mg/(kg·d) (large dose) and 1 mg/(kg·d) (small dose) intragastric administration, respectively, and the old control group was given equal volume of normal saline intragastric administration. The rats in each group were weighed once a week, and the dose was adjusted according to the change of body weight level. The rats in each group were given gavage for 4 months to 24 months. At 24 months of age, there were 10 surviving rats in the aged control group, 13 in the low-dose atorvastatin group and 14 in the high-dose atorvastatin group. Another 5 3-month-old Wistar rats (half male and half female) were purchased as the young control group. The rats were weighed and numbered.

2.2.2 Biological sample processing

Rat ischemia-reperfusion model was established, ECG and hemodynamic parameters were measured and a number of physiological signal collection systems were connected. The rats were anesthetized by intraperitoneal injection of 10% uratan (0.1ml/kg), and the body mass of the rats was recorded after satisfactory anesthesia. The rats were fixed on the experimental table, and the cardiac leads were connected and recorded [3]. The hair on the neck and chest was cut off, and iodophor was disinfected, the neck skin of the rats was cut lengthwise, the subcutaneous tissue and muscle were bluntly separated, the trachea was fully exposed, and the carotid artery was separated paratracheal. The airway wall was cut laterally in the cartilage space of trachea, and the animal ventilator was connected. The ventilation rate was 70 times/min, and the suction/breathing ratio was 1.25/1. The left ventricular systolic blood pressure (LVSP), left ventricular diastolic blood pressure (LVEDP), and the maximum rate of increase and decrease of left ventricular systolic blood pressure (±dp/dtmax) were recorded by a multichannel physiograph connected by a transducer. The thoracic skin was incised longitudinally along the left margin of the sternum, and the subcutaneous, pectoralis major and serratus anterior muscles were bluntly separated. Gradually cut the intercostal muscles to expose the pleura. Hemostasis is sufficient. Puncture the pleura on exhalation, stretch the ribs, tear the pericardium and expose the heart. The left atrial appendage was explored, and the ligation line was crossed about 2 mm below the left atrial appendage junction of the pulmonary conus. A plastic tube was inserted inside the line junction, and the line junction was tightened. ST segment elevation was observed in ECG records, and the color of myocardial tissue was darkened to determine the success of ligation. 30 min later, the plastic tube was pulled out and the coronary artery was recirculated for 30 min. Local tissue congestion occurred during reperfusion. Blood samples were taken before ischemia, 30min of ischemia, and 30min of reperfusion. Finally, the myocardial infarction area after ischemia reperfusion was determined, and the liver and kidney function of rats were detected, including GPT, GOT, Cr and BUN.

2.3 Statistical Methods

SPSS 25.0 statistical software was used for data analysis, measurement data were expressed as mean ± standard
deviation, and comparison between the two groups was conducted by t test. \( \chi^2 \) test was used for comparison between groups, and \( P<0.05 \) was considered statistically significant.

3. Results

3.1 Results of myocardial infarction size measurement

The myocardial infarction area of atorvastatin group was smaller than that of ischemia-reperfusion group, and the myocardial infarction area of atorvastatin group was larger than that of ischemia-reperfusion group, and the difference was statistically significant (\( P<0.05 \)). The total ischemic area (the sum of infarct area and ischemia-uninfarcted area) in atorvastatin group was smaller than that in ischemia-reperfusion group, and the difference was not statistically significant (\( P>0.05 \)). The proportion of myocardial infarction area to total ischemic area in atorvastatin group was smaller than that in ischemic reperfusion group, with statistical significance (\( P<0.001 \)), as shown in Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Myocardial infarct ratio (%)</th>
<th>Ischemic not myocardial infarct ratio (%)</th>
<th>Ischemic myocardial infarct ratio (%)</th>
<th>Myocardial infarct size/ischemic myocardium size (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>15</td>
<td>15.94±2.02</td>
<td>35.79±6.32</td>
<td>51.73±9.72</td>
<td>30.82±7.45</td>
</tr>
<tr>
<td>Ischemia reperfusion</td>
<td>15</td>
<td>26.49±1.94</td>
<td>23.04±4.93</td>
<td>49.52±5.35</td>
<td>53.49±10.91</td>
</tr>
</tbody>
</table>

3.2 Content determination of MDA, TNF-\( \alpha \) and MPO

Compared with sham operation group, MDA, TNF-\( \alpha \) and MPO were increased in ischemia-reperfusion group and atorvastatin group, and the difference was statistically significant (\( P<0.005 \)). Compared with the ischemia-reperfusion group, MDA, TNF-\( \alpha \) and MPO in the atorvastatin group were decreased, with statistical significance (\( p<0.05 \)), as shown in Table 2.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MDA</th>
<th>TNF-( \alpha )</th>
<th>MPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-operated</td>
<td>15</td>
<td>5.71±1.44</td>
<td>17.92±2.06</td>
<td>3.49±0.99</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>15</td>
<td>15.49±3.58</td>
<td>42.16±4.99</td>
<td>19.85±3.82</td>
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<tr>
<td>Ischemia reperfusion</td>
<td>15</td>
<td>10.02±2.18</td>
<td>32.49±2.79</td>
<td>13.25±1.33</td>
</tr>
</tbody>
</table>

3.3 Results of ventricular remodeling measurements

There was no significant difference in body weight among all groups (\( P>0.05 \)). Compared with the sham operation group, the relative weight of left and right ventricles in the ischemia-reperfusion group was larger and the thickness of ventricular septum was wider, and the differences were statistically significant (\( p<0.05 \)). Compared with the ischemia-reperfusion group, the relative mass of left and right ventricle and the thickness of ventricular septum in the atorvastatin group were smaller, and the differences were statistically significant (\( p<0.05 \)), as shown in Table 3.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>BW</th>
<th>LVRW</th>
<th>RVRW</th>
<th>IVST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-operated</td>
<td>15</td>
<td>372.9±40.8</td>
<td>1.45±0.22</td>
<td>0.44±0.10</td>
<td>1.82±0.31</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>15</td>
<td>349.6±55.5</td>
<td>2.33±0.41</td>
<td>0.70±0.24</td>
<td>2.61±0.42</td>
</tr>
<tr>
<td>Ischemia reperfusion</td>
<td>15</td>
<td>358.3±69.4</td>
<td>1.91±0.33</td>
<td>0.55±0.18</td>
<td>2.21±0.36</td>
</tr>
</tbody>
</table>

4. Discussion

Statins are widely used as lipid-regulating drugs. Studies have shown that statins can reduce the level of myocardial injury after myocardial ischemia-reperfusion surgery and improve long-term prognosis. The results of this
study showed that there was no difference in total ischemic area between the atorvastatin intervention group and the pure reperfusion group, but the myocardial infarction area of the atorvastatin intervention group was smaller than that of the ischemia-reperfusion [4] group, the ischemia-uninfarct area was larger than that of the ischemia-reperfusion group, and the ratio of myocardial infarction area to total ischemic area was smaller than that of the ischemia-reperfusion group, with statistical significance, which was consistent with the results of Post et al. The significant increase of free radicals is closely related to myocardial injury after ischemia reperfusion [5]. As the end product of lipid peroxides, MDA content can reflect the degree of oxygen free radical damage. The results of this study showed that compared with the sham operation group, the ischemia-reperfusion group was better than atorvastatin group. MDA in the statin group was increased, but the increase in the atorvastatin group was less than that in the ischemia-reperfusion group, which was consistent with the results of previous studies [6]. TNF-α is an important inflammatory cytokine, which can be aggravated by promoting the generation of oxygen free radicals and inducing cardiomyocyte apoptosis by activating granulocyte. The results of this study showed that the measurement results of ventricular remodeling with atorvastatin showed that the application of atorvastatin could effectively inhibit left ventricular dilation after ischemia reperfusion, improve left ventricular function, and reduce myocardial injury caused by reperfusion.

5. Conclusion

In conclusion, atorvastatin can affect the infarct size after myocardial ischemia-reperfusion injury and improve hemodynamics and left ventricular function, which provides an important theoretical basis for further research on the treatment of myocardial IRI with statins.

Ethics

All patients in this study were clearly aware of the specific content of the study, and the signing of relevant in formed consent was improved. The study was reviewed and approved by the ethics committee of the hospital.

References


